PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 17 October 1996 (17.10.96)	
International application No. PCT/GB96/00575	**Applicant's or agent's file reference** MBUS 1126A PCT
International filing date (day/month/year) 19 March 1996 (19.03.96)	**Priority date** (day/month/year) 25 March 1995 (25.03.95)
Applicant MURRER, Barry, Anthony et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

30 September 1996 (30.09.96)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Peggy Steunenberg
Facsimile No.: (41-22) 740 14 35	Telephone No.: (41-22) 730 91 11

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:
WISHART, Ian C.
JOHNSON MATTHEY plc.
Technology Centre
Blounts Court
Sonning Common
Reading RG4 9NH
GRANDE BRETAGNE

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	20.05.97

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
MBUS 1126A PCT	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB 96/00575	19/03/1996	25/03/1995

Applicant

JOHNSON MATTHEY PUBLIC LIMITED COMPANY et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Thulin Ben Thlija
	Telephone No.

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
MBUS 1126A PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB 96/ 00575	19/03/1996	25/03/1995
International Patent Classification (IPC) or national classification and IPC		
A61K33/24		
Applicant		
JOHNSON MATTHEY PUBLIC LIMITED COMPANY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This **REPORT** consists of a total of 3 sheets, including this cover sheet.

   ☒ This report is also accompanied by **ANNEXES**, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consists of a total of 1 sheets.

3. This report contains indications and corresponding pages relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30/09/1996	20.05.97
Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Cattell Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 1-8	YES
	Claims 9	NO
Inventive Step (IS)	Claims 1-6	YES
	Claims 7, 8	NO
Industrial Applicability (IA)	Claims 1-9	YES
	Claims	NO

2. CITATIONS AND EXPLANATIONS

1). Document D1 (Naohisa et al 1991) discloses on page 22 Table 2 $La_2(CO_3)_3:5H_2O$.
Document D2 (Chem abs; 107-249009) discloses $La_2(CO_3)_3.3H_2O$, as does Document D4 (Chem abs,87-161013
Document D3 (Chem abs;104-236218) discloses $La_2(CO_3)_3.6H_2O$.
These compounds fall within the scope of claim 9 under Article 33(2) PCT

2). D3 describes the preparation of La carbonate by reacting the nitrate with an alkali metal carbonate.
This disclosure would seem to render the reaction of claims 7 and 8 obvious under Article 33(3) PCT.

3). None of the cited documents indicate a pharmaceutical use of the claimed compounds, which is superior to the known forms of carbonate (see description Table 19 claims 1 to 6 would therefore appear to meet the requirements of Article 33 PCT.

Intern. application No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

PCT/GB96/00575

I. Basis of the report

1. This report has been drawn up on the basis of (Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.):

[ ] the international application as originally filed.

[x] the description, pages 1-13, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____,

[x] the claims, Nos. 1-6, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. 7-9, filed with the letter of 12.02.97,
Nos. _____, filed with the letter of _____,

[x] the drawings, sheets/fig 1-4, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:
[ ] the description, pages _____.
[ ] the claims, Nos. _____.
[ ] the drawings, sheets/fig _____.

3. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

PATENT COOPERATION TREATY

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REC'D 22 MAY 1997
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
MBUS 1126A PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB 96/ 00575	19/03/1996	25/03/1995
International Patent Classification (IPC) or national classification and IPC		
A61K33/24		
Applicant		
JOHNSON MATTHEY PUBLIC LIMITED COMPANY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets, including this cover sheet.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consists of a total of 1 sheets.

3. This report contains indications and corresponding pages relating to the following items:

   I [X] Basis of the report
   II [ ] Priority
   III [ ] Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   IV [ ] Lack of unity of invention
   V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   VI [ ] Certain documents cited
   VII [ ] Certain defects in the international application
   VIII [ ] Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30/09/1996	20.05.97
Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Cattell Telephone No.

Form PCT/IPEA/409 (cover sheet) (January 1994) (12/11/1996)

7. A process for the preparation of lanthanum carbonate as defined in any one of claims 1 to 3 which comprises the steps of:

(i) reacting lanthanum oxide with an acid which gives a soluble salt of lanthanum;

(ii) reacting a solution of the thus obtained lanthanum salt with an alkali metal carbonate to produce a wet cake of lanthanum carbonate octahydrate; and

(iii) controlled drying of the wet cake of lanthanum carbonate octahydrate so as to obtain a lanthanum carbonate with 3 to 6 molecules of water of crystallisation.

8. A process as claimed in claim 7 wherein the acid is nitric acid or hydrochloric acid.

9. A process as claimed in claim 7 or 8 wherein the alkali metal carbonate is sodium carbonate.

10. Lanthanum carbonate prepared according to the process of any of claims 7, 8 or 9.

11. Lanthanum carbonate of the formula

$$La_2(CO_3)_3.xH_2O$$

where x has a value from 3 to 6.

PATENT COOPERATION TREATY

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
MBUS 1126A PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB96/00575	19/03/96	25/03/95
Applicant		
JOHNSON MATTHEY PUBLIC LIMITED COMPANY et al.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [ ] the text is approved as submitted by the applicant.
   - [X] the text has been established by this Authority to read as follows:

   PHARMACEUTICAL COMPOSITION CONTAINING SELECTED LANTHANUM CARBONATE HYDRATES

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [ ] None of the figures.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 33/24 | A1

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Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PHARMACEUTICAL COMPOSITION CONTAINING SELECTED LANTHANUM CARBONATE HYDRATES

(57) Abstract

Selected lanthanum carbonate hydrates may be administered into the gastrointestinal tract, to treat hyperphosphataemia in patients with renal failure.

FOR THE PURPOSES OF INFORMATION ONLY

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PHARMACEUTICAL COMPOSITION CONTAINING SELECTED LANTHANUM CARBONATE HYDRATES

This invention concerns a novel and inventive pharmaceutical composition and method, more particularly it concerns a composition for the treatment of hyperphosphataemia.

Hyperphosphataemia is a particular problem of patients with renal failure, using dialysis equipment. Conventional dialysis fails to reduce levels of phosphate in the blood, so that the levels rise in time. It is known to control phosphate levels by the oral administration of aluminium salts, or calcium salts. With the known toxic effects of aluminium, aluminium-based therapy tends to be avoided. In the case

of calcium salts, calcium is absorbed rather readily from the gut, and in turn causes hypercalcaemia.

It has been suggested (Nakagawa *et al*, Trans Am Soc Intern Organs, 31, (1985) 155-9) that hydrous cerium oxide could be used as a bead in an ion-exchange column, to bind phosphate during dialysis. Japanese published patent application 61 004 529 appears to cover the same idea, suggesting that the hydrous oxides of La, Ce and Y may be used in the column. However, although the rare earths are generally considered of low toxicity according to the Hodge-Sterner classification system (Am Ind Hyg Assoc Quart, 10, (1943), 93), their toxicity when given *iv*, which corresponds to use in a blood dialysis system, is significant and we are not aware that the suggested ion exchange system or any development thereof has met with widespread acceptance or has been tested clinically for hyperphosphataemia.

It appears that cerium oxide or oxalate was administered many years ago for different medical indications, but that this has fallen into complete disuse.

Japanese published patent application number 62-145024 (Asahi Chemical Ind KK) discloses that rare earth carbonates, bicarbonates or organic acid compounds may be used as phosphate binding agents. One example of said published application relates to the use of lanthanum carbonate, although in the tests described, cerium organic acid salts and carbonate gave better phosphate ion extraction than lanthanum carbonate. Example 11 of said published application prepares

$La_2(CO_3)_3.H_2O$, *ie* the monohydrate; all the other Examples are directed to rare earth carbonates other than lanthanum carbonate.

We have now discovered that certain forms of lanthanum carbonate exhibit improved performance in a variety of tests, over standard commercial lanthanum carbonate, which is believed to be the octahydrate form, and over $La_2(CO_3)_3.H_2O$ or similar compounds.

According to one aspect therefore, the present invention is the use of lanthanum carbonate of formula $La_2(CO_3)_3.xH_2O$ where x has a value from 3 to 6, preferably from 3.5 to 5, more especially from 3.8 to 4.5, for the preparation of a medicament for the treatment of hyperphosphataemia by administration into the gastrointestinal tract.

The invention further provides a pharmaceutical composition comprising said lanthanum carbonate, in admixture or association with a pharmaceutically acceptable diluent or carrier, in a form for administration into the gastrointestinal tract for the treatment of hyperphosphataemia.

The invention may also be expressed as a method of treatment of hyperphosphataemia in a patient with renal failure, comprising the administration of an effective dose of said lanthanum carbonate into the gastrointestinal tract.

According to another aspect, the present invention is a process for the preparation of lanthanum carbonate which comprises the steps of:

(i) reacting lanthanum oxide with an acid which gives a soluble salt of lanthanum;

(ii) reacting a solution of the thus obtained lanthanum salt with an alkali metal carbonate to produce a wet cake of lanthanum carbonate octahydrate; and

(iii) controlled drying of the wet cake of lanthanum carbonate octahydrate so as to obtain a lanthanum carbonate with 3 to 6 molecules of water of crystallisation.

According to yet another aspect, the present invention is lanthanum carbonate when obtained by the above-mentioned process.

According to a further aspect, the present invention is lanthanum carbonate of the formula $La_2(CO_3)_3.xH_2O$ where x has a value from 3 to 6.

Embodiments of the present invention are described below, by way of example only, with reference to the accompanying drawings in which:

Figure 1 illustrates the phosphate-binding capability of lanthanum carbonates having different degrees of water of crystallisation;

Figure 2 illustrates the drying curves for five batches of lanthanum carbonate prepared by the method indicated in Example 1;

Figure 3 illustrates the XRD analysis of lanthanum carbonate $4H_2O$ prepared by the method indicated in Example 2; and

Figure 4 illustrates the XRD analysis of lanthanum carbonate $8.8H_2O$ of Sample 1 above.

For the tests described hereinafter, samples of lanthanum carbonate were obtained as follows:

Sample 1. Commercial lanthanum carbonate obtained from a chemical company. This was characterised by elemental analysis (La, C, H), TGA, X-ray powder diffraction and ir spectroscopy, to have the formula $La_2(CO_3)_3.8.8H_2O$.

Samples 2 - 4 were prepared by heating portions of Sample 1 at varying temperatures for varying lengths of time, either under vacuum or at atmospheric pressure to obtain materials of formula $La_2(CO_3)_3.xH_2O$ where $0 < x < 8$.

Sample	Initial wt (g)	Temp (°C)	Time (min)	Vacuum (Y/N)	Wt loss (g)	x
2	5.00	175	240	Y	1.09	1.3
3	20.0	80	180	N	2.6	4.4
4	5.01	100	720*	N	0.96	2.2

* Dried to constant weight.

Sample 5 is a sample of lanthanum carbonate which when analysed indicated a formula of $La_2(CO_3)_3.4H_2O$.

Sample 6 is a sample of lanthanum carbonate prepared according to Example 1 below and having the formula $La_2(CO_3)_3.3.8H_2O$.

In order to show that certain lanthanum carbonate hydrates are significantly different in phosphate binding activity from both lanthanum carbonate octahydrate and from $La_2(CO_3)_3.H_2O$, samples were tested as follows:

i) a stock solution was prepared by dissolving 13.75g of anhydrous Na_2HPO_4, 8.5g of NaCl in 1 litre deionised water.

ii) 100ml of the stock solution was adjusted to pH3 by the addition of concentrated HCl.

iii) A 5ml sample was taken and filtered through a 0.02μm filter to give a Time 0 sample. This was analysed for phosphate using a Sigma Diagnostics Colorimetric Phosphorus test kit.

iv) 5ml fresh stock solution was added to re-establish 100ml, and the pH was re-adjusted to approximately 3.

v) $La_2(CO_3)_3.xH_2O$ as a dry powder was added in an amount according to the molecular weight of the particular hydrate, to give a two-fold molar excess of lanthanum over phosphate and stirred at room temperature.

vi) Sampling was carried out at time intervals from 0.5 to 10 minutes, and the percentage of phosphate was determined as in iii) above. The results are shown in the Table 1 below.

TABLE 1

TIME (Minutes)	% PHOSPHATE REMOVED Sample					
	1	2	3	4	5	6
0						
0.5		13.4	18.8	15.1	22.9	31.4
1	29	18.4	31.5	26.8	40.4	55.5
1.5		25.4	43.1	36	55.2	74.8
2		28.1	50.6	45.3	69.5	88.1
2.5		30.8	60.5	51.8	79.9	95.3
3		34.4	69	57.6	90.3	99.6
4						100
5	70.5	39.9	96.5	76.3	100	100
10	100	ND	99.1	ND	100	100

It can readily be seen from Table 1 that Sample 3 ($La_2(CO_3)_3.4.4H_2O$); Sample 5 ($La_2(CO_3)_3.4H_2O$) and Sample 6 ($La_2(CO_3)_3.3.8H_2O$) bind phosphate appreciably quicker than the $8.8H_2O$, $.1.3H_2O$ or $2.2H_2O$ forms. We believe that the results for $La_2(CO_3)_3.1.3H_2O$ are in agreement with the results shown in the above mentioned Japanese published patent application number 62-145024 where for $La_2(CO_3)_3.H_2O$, only 90% removal is shown after 120 minutes.

It can also be readily seen from Figure 1 of the accompanying drawings that the highest phosphate removal is obtained with lanthanum carbonates having 3 to 6 molecules of water.

The present invention offers the possibility of binding phosphate without any incursion of lanthanum into the blood stream, where toxic effects can cause problems. The specified lanthanum carbonate has negligible absorption from the gut, as shown by the *in vivo* tests described below.

Throughout this document, the term "treatment" is intended to include preventative treatment.

Processes for preparing lanthanum carbonates according to the present invention are described by way of illustration in the following Examples 1 and 2.

EXAMPLE 1

Lanthanum oxide (1.5kg, 4.58mol) was suspended in water (5.5 litres) in a 20 litre flask. Nitric acid (Analar grade, 69%, SG 1.42, 1.88 litres, 29.23mol) was added to the stirred solution over 1.5 hours at such a rate as to keep the temperature between 60-80°C. The resulting lanthanum nitrate solution was left to cool to room temperature and filtered. A solution of sodium carbonate (1.65kg, 15.57mol) in water (7.75 litres) was added to the stirred lanthanum nitrate solution over 45 minutes. At the end of the addition the pH of the suspension was 9.74. The suspension was left

overnight, filtered (Buchner funnel, 540 paper) and dried on the filter in a current of air for 30 minutes. The solid was then re-suspended in water, stirred for 40 minutes and filtered. This procedure was repeated to give a total of six washes, when the nitrate concentration in the filtrate was <500ppm. The final material (4.604kg) was divided between three Pyrex dishes and a sample from each analysed for water content. (By decomposition of weighed sample of $(La_2(CO_3)_3.xH_2O$ at 1050°C, 2 hours to La_2O_3). The dishes were then placed in a fan oven at 80°C and the weight loss of each dish monitored until the material of the required degree hydration was obtained. The progress of the drying is shown below

Time (hours)	mol H_2O/La		
	Dish 1	Dish 2	Dish 3
3.50	10.9	13.5	12.6
12	5.7	6.0	5.2
14	5.3	5.4	4.6
16	4.9	5.1	4.3
17	4.4	4.6	3.8
19.5	3.8	4.0	3.2

Drying curves for five batches produced by this route are shown in Figure 2.

$La_2(CO_3)_3.3.8H_2O$ from dish 1 was selected as Sample 6 for the phosphate binding tests set forth in Table 1.

EXAMPLE 2

The process of Example 1 was repeated but using hydrochloric acid (12.28M, 2.48 litres) in place of nitric acid to dissolve lanthanum oxide (1.5kg). The yield of crude product after six washes was 4.378kg. The product was divided in three approximately equal portions in Pyrex dishes and dried in a fan oven at 80°C. After 2 hours a sample was taken from each tray and water analysed by decomposition to lanthanum oxide as described above. These figures were used to calculate the weight loss needed to give material of the required composition. The time course of the drying process is shown below.

Time (hours)	mol H_2O/La		
	Dish 1	Dish 2	Dish 3
2	21.3	22.1	20.4
5.5	12.3	13.2	12.2
9	7.9	8.0	7.6
11.5	6.9	7.0	6.6
17	4.9	5.1	4.6
18.5	4.6	4.8	4.2
19.5	4.4	4.6	4.1
20	4.3	4.6	4.0

Samples were taken from each dish, combined and analysed. The following results were obtained:

	Found	Calculation for $La_2(CO_3)_3.4H_2O$
% La (gravimetric)	52.38%	52.4%
carbonate (titration)	5.76mol/g	5.66mol/g
H_2O (NMR)	13.06%	13.59%

The XRD analysis for lanthanum carbonate $4H_2O$ prepared by the method of Example 2 is illustrated in Figure 3.

Figure 4 illustrates the XRD of lanthanum carbonate $8.8H_2O$ and it is evident that it has a different crystalline structure from lanthanum carbonate $4H_2O$ prepared by the method of Example 2. The XRD analysis of lanthanum carbonate $4H_2O$ prepared by the method of Example 1 was similar to the XRD analysis of lanthanum carbonate $4H_2O$ prepared by the method of Example 2.

Pharmaceutical compositions for oral administration according to the invention may be formulated and manufactured using methods well known in the art. Suitable diluents or carriers are also well known. The compositions may desirably be in a dosage form, to provide a single daily dose, or a number of sub-daily dosages. Conventional pharmacological methods may be used to ascertain suitable dose levels. The level of phosphate in the food that an individual ingests is important. Daily dosages are indicated to be in the range 0.1 to 50g, preferably about 0.5 to 15g. Suitable forms for oral administration include solid forms such as tablets, capsules and dragees and liquid forms such as suspensions or syrups. In addition to diluents and carriers, it is conventional in the formulation of oral preparations to include non-active

ingredients such as thickeners, taste-improving components and colouring agents. The said carbonate may also be coated or treated to provide delayed-release forms. Preferably, the required daily dosage is given in tablet form, *eg* chewable tablet form, to be taken with meals. A suitable daily dosage of about 2g for 70kg man, should be compared with a daily dosage of 20g for a commercial calcium-based phosphate binding composition.

To demonstrate that the lanthanum carbonate of the invention (or lanthanum phosphate formed after binding to phosphate in the gut) is fully excreted and does not pass out of the gut into the circulation system when given orally, three rats were dosed with 20mg/kg of $La_2(CO_3)_3.4H_2O$ (Sample 5) and kept in metabolic cages where faeces and urine could be collected. The results are shown in Table 2 below.

Animal No.	Time (hours)	% La Recovered
1	24	103.2
1	48	0.1
1	72	<0.2
1	Total	103.3
2	24	75.3
2	48	23
2	72	1.2
2	Total	99.5

Animal No	Time (hours)	%La Recovered
3	24	93.8
3	48	10
3	72	0.1
3	Total	103.8

It can be seen that after 72 hours, all of the lanthanum has been excreted. In the urine samples, the amount of lanthanum was below detection limits. After the test, the rats were sacrificed, and kidney, liver and femur were analysed for lanthanum. In all cases, the amount of lanthanum was below 0.1ppm.

CLAIMS

1. A pharmaceutical composition for the treatment of hyperphosphataemia, comprising lanthanum carbonate of formula

$$La_2(CO_3)_3.xH_2O$$

where x has a value from 3 to 6, in admixture or association with a pharmaceutically acceptable diluent or carrier.

2. A composition according to claim 1, wherein in the lanthanum carbonate, x has a value from 3.5 to 5.

3. A composition according to claim 2, wherein in the lanthanum carbonate, x has a value from 3.8 to 4.5.

4. A composition according to any one of claims 1 to 3, in a form suitable for oral administration.

5. A composition according to any one of claims 1 to 4 in unit dosage form to provide from 0.1 to 20g/day.

6. The use of lanthanum carbonate as defined in any one of claims 1 to 3, for the preparation of a medicament for the treatment of hyperphosphataemia by administration into the gastrointestinal tract.

7. A process for the preparation of lanthanum carbonate as defined in any one of claims 1 to 3 which comprises the steps of:

(i) reacting lanthanum oxide with an acid which gives a soluble salt of lanthanum;

(ii) reacting a solution of the thus obtained lanthanum salt with an alkali metal carbonate to produce a wet cake of lanthanum carbonate octahydrate; and

(iii) controlled drying of the wet cake of lanthanum carbonate octahydrate so as to obtain a lanthanum carbonate with 3 to 6 molecules of water of crystallisation.

8. A process as claimed in claim 7 wherein the acid is nitric acid or hydrochloric acid.

9. A process as claimed in claim 7 or 8 wherein the alkali metal carbonate is sodium carbonate.

10. Lanthanum carbonate prepared according to the process of any of claims 7, 8 or 9.

11. Lanthanum carbonate of the formula

$$La_2(CO_3)_3.xH_2O$$

where x has a value from 3 to 6.

Fig. 1

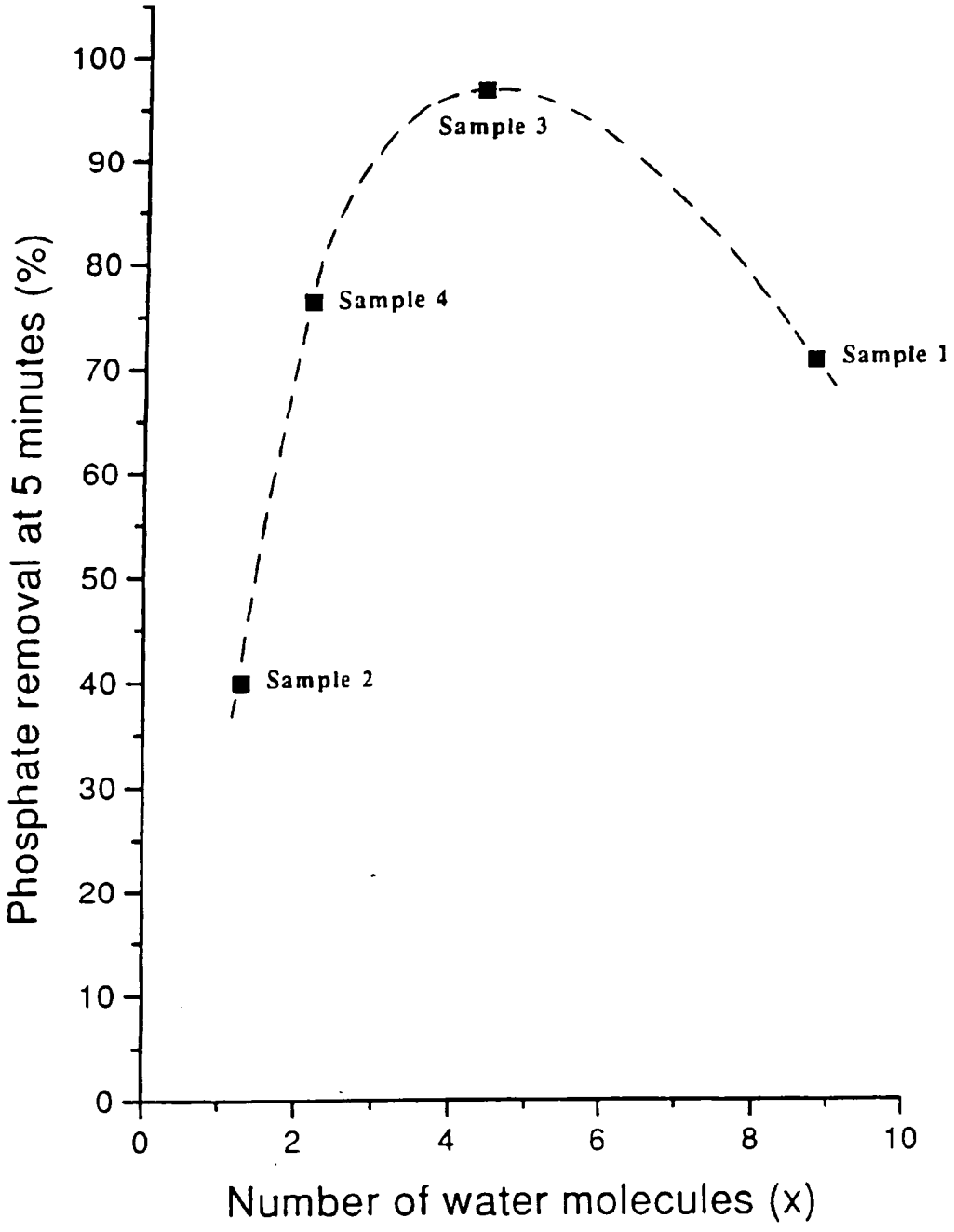

Phosphate removal at 5 minutes (%)
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
Number of water molecules (x)
Sample 3
Sample 4
Sample 1
Sample 2

Fig. 2

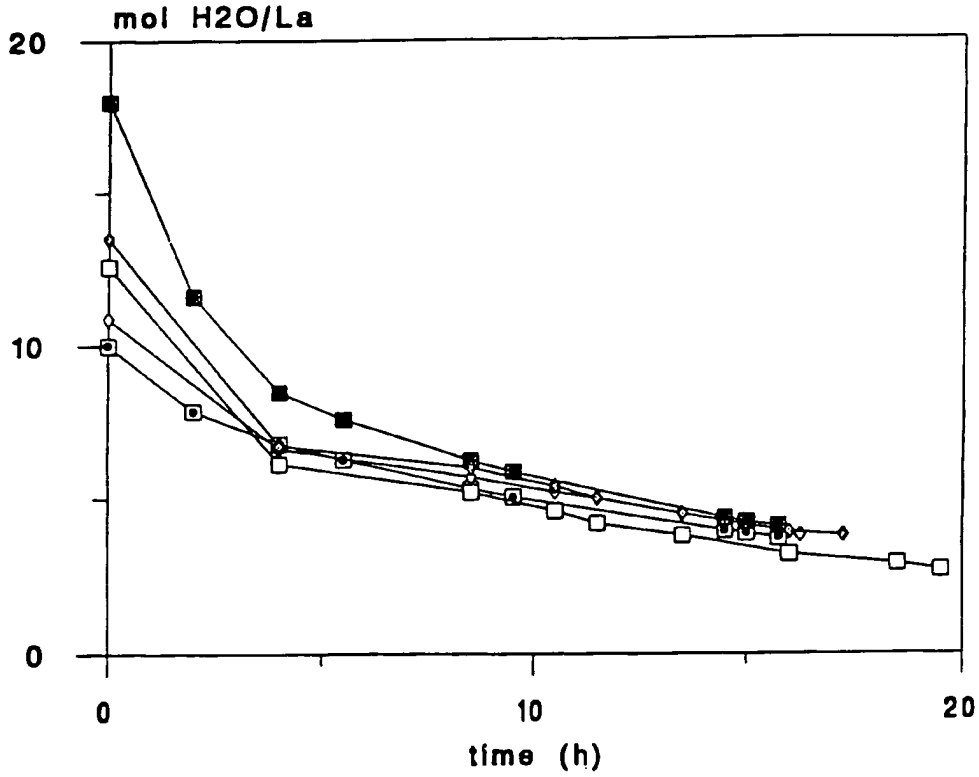


Fig. 3

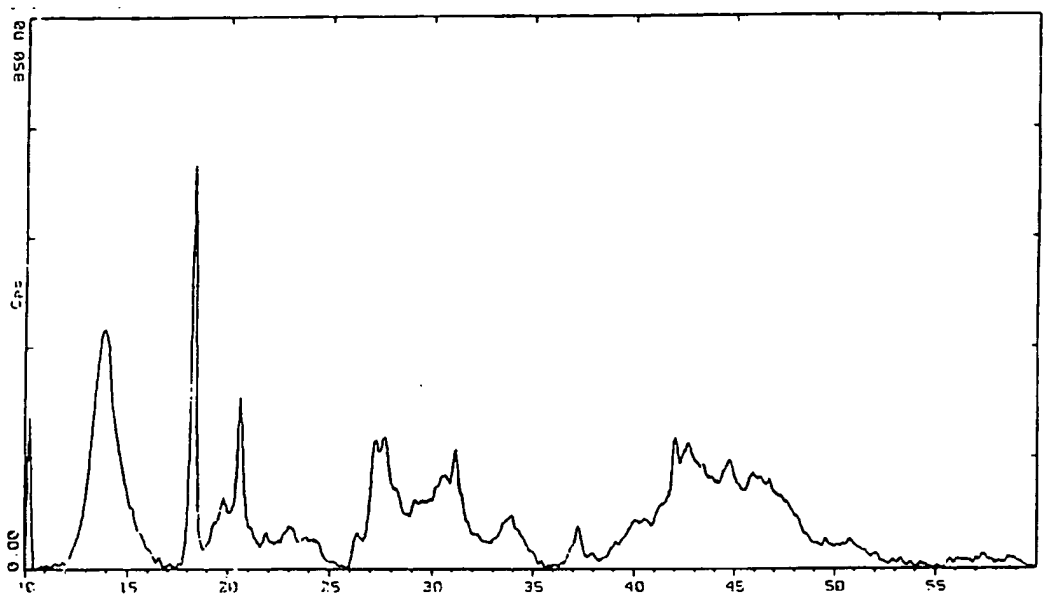
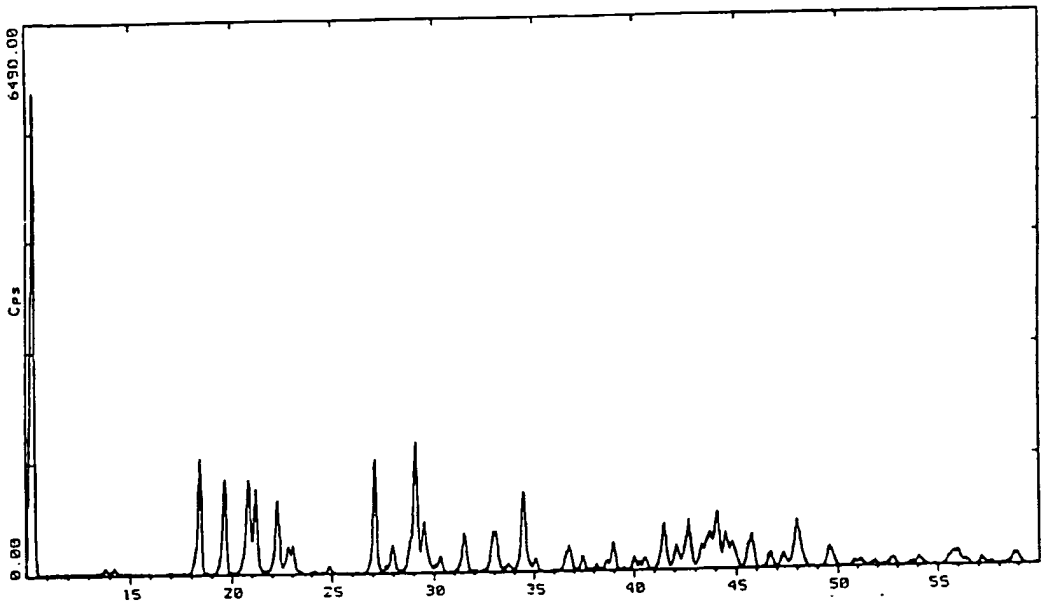


Fig.4



MBUS 1126A

PHARMACEUTICAL COMPOSITION AND METHOD

This invention concerns a novel and inventive pharmaceutical composition and method, more particularly it concerns a composition for the treatment of hyperphosphataemia.

Hyperphosphataemia is a particular problem of patients with renal failure, using dialysis equipment. Conventional dialysis fails to reduce levels of phosphate in the blood, so that the levels rise in time. It is known to control phosphate levels by the oral administration of aluminium salts, or calcium salts. With the known toxic effects of aluminium, aluminium-based therapy tends to be avoided. In the case of calcium salts, calcium is absorbed rather readily from the gut, and in turn causes hypercalcaemia.

It has been suggested (Nakagawa *et al*, Trans Am Soc Intern Orga., 31, (1985) 155-9) that hydrous cerium oxide could be used as a bead in an ion-exchange column, to bind phosphate during dialysis. Japanese published patent application 61 004 529 appears to cover the same idea, suggesting that the hydrous oxides of La, Ce and Y may be used in the column. However, although the rare earths are generally considered of low toxicity according to the Hodge-Sterner classification system (Am Ind Hyg Assoc Quart, 10, (1943), 93), their toxicity when given *iv*, which corresponds to use in a blood dialysis system, is significant and we are not aware that the suggested ion exchange system or any development thereof has met with widespread acceptance or has been tested clinically for hyperphosphataemia.

It appears that cerium oxide or oxalate had been administered many years ago for different medical indications, but that this has fallen into complete disuse.

Japanese published patent application number 62-145024 (Asahi Chemical Ind KK) discloses that rare earth carbonates, bicarbonates or organic acid compounds may be used as phosphate binding agents. One example relates to the use of lanthanum carbonate, although in the tests described, cerium organic acid salts and carbonate gave better phosphate ion extraction than lanthanum carbonate. (It is our view that the tests described are not representative of conditions in the gastrointestinal tract, since measurements are taken at pH7.) Example 11 of said

published application prepares $La_2(CO_3)_3.H_2O$, that is a monohydrate; all other Examples are quite specific as to the amount of water of crystallisation.

We have now discovered that certain forms of lanthanum carbonate exhibit improved performance in a variety of tests, over standard commercial lanthanum carbonate, which is believed to be the octahydrate form, and over $La_2(CO_3)_3.H_2O$ or similar compounds.

A form which analyses as the tetrahydrate form may be prepared by heating the octahydrate for sufficient time to drive off 4 molecules of water of crystallisation per mol of lanthanum carbonate, *eg* 60 to 80°C for 2 hours. An amorphous solid is obtained. Other routes for preparation of the tetrahydrate form may be used, or there may be commercial sources, although commercial sources do not usually analyse for water of crystallisation.

For the tests described hereinafter, samples of lanthanum carbonate were obtained as follows:

Sample 1. Commercial lanthanum carbonate obtained from a chemical company. This was characterised by elemental analysis (La, C, H), TGA, X-ray powder diffraction and ir spectroscopy, to have the formula $La_2(CO_3)_3.8.8H_2O$.

Samples 2 - 4 were prepared by heating portions of Sample 1 at varying temperatures for varying lengths of time, either under vacuum or at atmospheric pressure to obtain materials of formula $La_2(CO_3)_3.xH_2O$ where $0 < x < 8$.

Sample	Initial wt (g)	Temp (°C)	Time (min)	Vacuum (Y/N)	Wt loss (g)	x
2	5.00	175	240	Y	1.09	1.3
3	20.0	80	180	N	2.6	4.4
4	5.01	100	720*	N	0.96	2.2

* Dried to constant weight.

A sample of $La_2(CO_3)_3.4H_2O$ was obtained and allocated Sample number 5.

In order to show that lanthanum carbonate tetrahydrate is significantly different in phosphate binding activity from both conventional, commercial lanthanum carbonate octahydrate and from $La_2(CO_3)_3.H_2O$, samples were tested as follows:

i) a stock solution was prepared by dissolving 13.75g of anhydrous Na_2HPO_4, 8.5g of NaCl in 1 litre 18MΩ water.

ii) 100ml of the stock solution was adjusted to pH3 by the addition of concentrated HCl.

iii) A 5ml sample was taken and filtered through a 0.02μm filter to give a Time 0 sample. This was analysed for phosphate using a Sigma Diagnostics Colorimetric Phosphorus test kit.

iv) 5ml fresh stock solution was added to re-establish 100ml, and the pH was re-adjusted to approximately 3.

v) $La_2(CO_3)_3.xH_2O$ as a dry powder was added in an amount according to the molecular weight of the particular hydrate, to give a two-fold molar excess of lanthanum over phosphate and stirred at room temperature.

vi) Sampling was carried out at time intervals from 0.5 to 10 minutes, and the percentage of phosphate was determined as in iii) above. The results are shown in the Table 1 below.

TABLE 1

	% PHOSPHATE REMOVED				
TIME (Minutes)	Sample				
	1	2	3	4	5
0					
0.5		13.4	18.8	15.1	22.9
1	29.0	18.4	31.5	26.8	404
1.5		25.4	43.1	36.0	55.2
2		28.1	50.6	45.3	69.5
2.5		30.8	60.5	51.8	79.9
3		34.4	69.0	57.6	90.3
5	70.5	39.9	96.5	76.3	100
10	100	ND	99.1	ND	100

It can readily be seen that Samples 3 and 5 ($La_2(CO_3)_3.4H_2O$ a... $La_2(CO_3)_3.4.4H_2O$) bind phosphate appreciably quicker than the $.8H_2O$ or $.1.3H_2O$ forms. We believe that these results are in agreement with the results shown in the said Japanese patent application where for $La_2(CO_3)_3.H_2O$, only 90% removal is shown after 120 mins.

We also believe that testing at pH3 is more representative of conditions in the upper gastrointestinal tract than pH7, and also that it is important to remove phosphate as early as possible in the digestion process.

The present invention offers the possibility of binding phosphate without any incursion of lanthanum into the blood stream, where toxic effects including, we believe, calcium antagonism, can cause problems. The specific lanthanum carbonate has negligible absorption from the gut, as shown by the *in vivo* tests described below.

Throughout this document, the term "treatment" is intended to include preventative treatment.

The present invention, therefore, is defined as the use of lanthanum carbonate of formula $La_2(CO_3)_3.xH_2O$ where x has a value from 3 to 6, preferably from 3.5 to 5, more especially from 3.9 to 4.5, for the preparation of a medicament for the treatment of hyperphosphataemia by administration into the gastrointestinal tract.

The invention further provides a pharmaceutical composition comprising said lanthanum carbonate, in admixture or association with a pharmaceutically acceptable diluent or carrier, in a form for administration into the gastrointestinal tract for the treatment of hyperphosphataemia.

The invention may also be expressed as a method of treatment of hyperphosphataemia in a patient with renal failure, comprising the administration of an effective dose of said lanthanum carbonate into the gastrointestinal tract.

Pharmaceutical compositions for oral administration according to the invention may be formulated and manufactured using methods well known in the art. Suitable diluents or carriers are also well known. The compositions may desirably be in a dosage form, to provide a single daily dose, or a number of sub-daily dosages. Conventional pharmacological methods may be used to ascertain suitable dose levels. The level of phosphate in the food that an individual ingests is important. Daily dosages are indicated to be in the range 1 to 50g, preferably about 1.5 to 15g. Suitable forms for oral administration include solid forms such as tablets, capsules and dragees and liquid forms such as suspensions or syrups. In addition to diluents and carriers, it is conventional in the formulation of oral preparations to include non-active ingredients such as thickeners, taste-improving components and colouring agents. The said carbonate may also be coated or treated to provide delayed-release forms. Preferably, the required daily dosage is given in tablet form, *eg* chewable tablet form, to be taken with meals. A suitable daily

dosage of about 2g for 70kg man, should be compared with a daily dosage of 2. for a commercial calcium-based phosphate binding composition.

To demonstrate that the lanthanum carbonate of the invention (or lanthanum phosphate) is fully excreted and does not pass out of the gut into the system when given orally, three rats were dosed with 20mg/kg of $La_2(CO_3)_3.4H_2O$ and kept in metabolic cages where faeces and urine could be collected. The results are shown in Table 2 below.

Animal No.	Time (hours)	% La Recovered
1	24	103.2
1	48	0.1
1	72	<0.2
1	Total	103.3
2	24	75.3
2	48	23.0
2	72	1.2
2	Total	99.5
3	24	93.8
3	48	10.0
3	72	0.1
3	Total	103.8

It can be seen that after 72 hours, all of the lanthanum has been excreted. In the urine samples, the amount of lanthanum was below detection limits.

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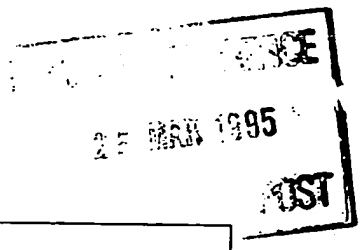
25 MAR 1995



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9506126.3

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Form 1/77

Patents Act 1977

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1 Please give the title of the invention

PHARMACEUTICAL COMPOSITION AND METHOD

❷ Applicant's details

☒ **First or only applicant**

2a If you are applying as a corporate body please give:

Corporate name

JOHNSON MATTHEY PUBLIC LIMITED COMPANY

Country *(and State of incorporation, if appropriate)* GB

2b If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2c **In all cases**, please give the following details:

Address 78 HATTON GARDEN
LONDON

UK postcode *(if applicable)* EC1N 8JP

Country GB

ADP number *(if known)* 5361680051

2d, 2e and 2f: *If there are further applicants please provide details on a separate sheet of paper.*

❑ **Second applicant** ***(if any)***

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Country *(and State of incorporation, if appropriate)*

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Yes [X] No [ ] ➡ ***go to 3b***

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Agent's address JOHNSON MATTHEY TECHNOLOGY CENTRE
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Agent's ADP number 39914737001

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Yes ☐ No [X] ➡ ***A Statement of Inventorship on Patents Form 7/77 will need to be filed (see Rule 15).***

❽ *Please supply duplicates of claim(s), abstract, description and drawing(s).*

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Continuation sheets for this Patents Form 1/77	NIL		
Claim(s)	1	Description	9
Abstract	1	Drawing(s)	

8b Which of the following documents also accompanies the application?

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❹ Reference number

4 Agent's or applicant's reference number *(if applicable)* MBUS 1126A

❺ Claiming an earlier application date

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After the test, the rats were sacrificed, and kidney, liver and femur were analysed for lanthanum. In all cases, the amount of lanthanum was below 0.1ppm.

CLAIMS

1. A pharmaceutical composition for the treatment of hyperphosphataemia, comprising lanthanum carbonate of formula

$$La_2(CO_3)_3.xH_2O$$

where x has a value from 3 to 6, in admixture or association with a pharmaceutically acceptable diluent or carrier.

2. A composition according to claim 1, wherein in the lanthanum carbonate, x has a value from 3.5 to 5.

3. A composition according to claim 2, wherein in the lanthanum carbonate, x has a value from 3.9 to 4.5.

4. A composition according to any one of claims 1 to 3, in a form suitable for oral administration.

5. A composition according to any one of claims 1 to 4 in unit dosage form to provide from 1 to 20g/day.

6. The use of lanthanum carbonate as defined in any one of claims 1 to 3, for the preparation of a medicament for the treatment of hyperphosphataemia by administration into the gastrointestinal tract.

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(71) Applicant *(for all designated States except US)*: JOHNSON MATTHEY PUBLIC LIMITED COMPANY [GB/GB]; 78 Hatton Garden, London EC1N 8JP (GB).

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(74) Agents: BREWER, Leonard, Stuart et al.; Johnson Matthey plc, Technology Centre, Blounts Court, Sonning Common, Reading RG4 9NH (GB).

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(54) Title: PHARMACEUTICAL COMPOSITION CONTAINING SELECTED LANTHANUM CARBONATE HYDRATES

(57) Abstract

Selected lanthanum carbonate hydrates may be administered into the gastrointestinal tract, to treat hyperphosphataemia in patients with renal failure.

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PHARMACEUTICAL COMPOSITION CONTAINING SELECTED LANTHANUM CARBONATE HYDRATES

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Hyperphosphataemia is a particular problem of patients with renal failure, using dialysis equipment. Conventional dialysis fails to reduce levels of phosphate in the blood, so that the levels rise in time. It is known to control phosphate levels by the oral administration of aluminium salts, or calcium salts. With the known toxic effects of aluminium, aluminium-based therapy tends to be avoided. In the case

of calcium salts, calcium is absorbed rather readily from the gut, and in turn causes hypercalcaemia.

It has been suggested (Nakagawa *et al*, Trans Am Soc Intern Organs, 31, (1985) 155-9) that hydrous cerium oxide could be used as a bead in an ion-exchange column, to bind phosphate during dialysis. Japanese published patent application 61 004 529 appears to cover the same idea, suggesting that the hydrous oxides of La, Ce and Y may be used in the column. However, although the rare earths are generally considered of low toxicity according to the Hodge-Sterner classification system (Am Ind Hyg Assoc Quart, 10, (1943), 93), their toxicity when given *iv*, which corresponds to use in a blood dialysis system, is significant and we are not aware that the suggested ion exchange system or any development thereof has met with widespread acceptance or has been tested clinically for hyperphosphataemia.

It appears that cerium oxide or oxalate was administered many years ago for different medical indications, but that this has fallen into complete disuse.

Japanese published patent application number 62-145024 (Asahi Chemical Ind KK) discloses that rare earth carbonates, bicarbonates or organic acid compounds may be used as phosphate binding agents. One example of said published application relates to the use of lanthanum carbonate, although in the tests described, cerium organic acid salts and carbonate gave better phosphate ion extraction than lanthanum carbonate. Example 11 of said published application prepares

$La_2(CO_3)_3.H_2O$, *ie* the monohydrate; all the other Examples are directed to rare earth carbonates other than lanthanum carbonate.

We have now discovered that certain forms of lanthanum carbonate exhibit improved performance in a variety of tests, over standard commercial lanthanum carbonate, which is believed to be the octahydrate form, and over $La_2(CO_3)_3.H_2O$ or similar compounds.

According to one aspect therefore, the present invention is the use of lanthanum carbonate of formula $La_2(CO_3)_3.xH_2O$ where x has a value from 3 to 6, preferably from 3.5 to 5, more especially from 3.8 to 4.5, for the preparation of a medicament for the treatment of hyperphosphataemia by administration into the gastrointestinal tract.

The invention further provides a pharmaceutical composition comprising said lanthanum carbonate, in admixture or association with a pharmaceutically acceptable diluent or carrier, in a form for administration into the gastrointestinal tract for the treatment of hyperphosphataemia.

The invention may also be expressed as a method of treatment of hyperphosphataemia in a patient with renal failure, comprising the administration of an effective dose of said lanthanum carbonate into the gastrointestinal tract.

According to another aspect, the present invention is a process for the preparation of lanthanum carbonate which comprises the steps of:

(i) reacting lanthanum oxide with an acid which gives a soluble salt of lanthanum;

(ii) reacting a solution of the thus obtained lanthanum salt with an alkali metal carbonate to produce a wet cake of lanthanum carbonate octahydrate; and

(iii) controlled drying of the wet cake of lanthanum carbonate octahydrate so as to obtain a lanthanum carbonate with 3 to 6 molecules of water of crystallisation.

According to yet another aspect, the present invention is lanthanum carbonate when obtained by the above-mentioned process.

According to a further aspect, the present invention is lanthanum carbonate of the formula $La_2(CO_3)_3.xH_2O$ where x has a value from 3 to 6.

Embodiments of the present invention are described below, by way of example only, with reference to the accompanying drawings in which:

Figure 1 illustrates the phosphate-binding capability of lanthanum carbonates having different degrees of water of crystallisation;

Figure 2 illustrates the drying curves for five batches of lanthanum carbonate prepared by the method indicated in Example 1;

Figure 3 illustrates the XRD analysis of lanthanum carbonate $4H_2O$ prepared by the method indicated in Example 2; and

Figure 4 illustrates the XRD analysis of lanthanum carbonate $8.8H_2O$ of Sample 1 above.

For the tests described hereinafter, samples of lanthanum carbonate were obtained as follows:

Sample 1. Commercial lanthanum carbonate obtained from a chemical company. This was characterised by elemental analysis (La, C, H), TGA, X-ray powder diffraction and ir spectroscopy, to have the formula $La_2(CO_3)_3.8.8H_2O$.

Samples 2 - 4 were prepared by heating portions of Sample 1 at varying temperatures for varying lengths of time, either under vacuum or at atmospheric pressure to obtain materials of formula $La_2(CO_3)_3.xH_2O$ where $0 < x < 8$.

Sample	Initial wt (g)	Temp (°C)	Time (min)	Vacuum (Y/N)	Wt loss (g)	x
2	5.00	175	240	Y	1.09	1.3
3	20.0	80	180	N	2.6	4.4
4	5.01	100	720*	N	0.96	2.2

* Dried to constant weight.

Sample 5 is a sample of lanthanum carbonate which when analysed indicated a formula of $La_2(CO_3)_3.4H_2O$.

Sample 6 is a sample of lanthanum carbonate prepared according to Example 1 below and having the formula $La_2(CO_3)_3.3.8H_2O$.

In order to show that certain lanthanum carbonate hydrates are significantly different in phosphate binding activity from both lanthanum carbonate octahydrate and from $La_2(CO_3)_3.H_2O$, samples were tested as follows:

i) a stock solution was prepared by dissolving 13.75g of anhydrous Na_2HPO_4, 8.5g of NaCl in 1 litre deionised water.

ii) 100ml of the stock solution was adjusted to pH3 by the addition of concentrated HCl.

iii) A 5ml sample was taken and filtered through a 0.02μm filter to give a Time 0 sample. This was analysed for phosphate using a Sigma Diagnostics Colorimetric Phosphorus test kit.

iv) 5ml fresh stock solution was added to re-establish 100ml, and the pH was re-adjusted to approximately 3.

v) $La_2(CO_3)_3.xH_2O$ as a dry powder was added in an amount according to the molecular weight of the particular hydrate, to give a two-fold molar excess of lanthanum over phosphate and stirred at room temperature.

vi) Sampling was carried out at time intervals from 0.5 to 10 minutes, and the percentage of phosphate was determined as in iii) above. The results are shown in the Table 1 below.

TABLE 1

TIME (Minutes)	% PHOSPHATE REMOVED					
	Sample					
	1	2	3	4	5	6
0						
0.5		13.4	18.8	15.1	22.9	31.4
1	29	18.4	31.5	26.8	40.4	55.5
1.5		25.4	43.1	36	55.2	74.8
2		28.1	50.6	45.3	69.5	88.1
2.5		30.8	60.5	51.8	79.9	95.3
3		34.4	69	57.6	90.3	99.6
4						100
5	70.5	39.9	96.5	76.3	100	100
10	100	ND	99.1	ND	100	100

It can readily be seen from Table 1 that Sample 3 ($La_2(CO_3)_3.4.4H_2O$); Sample 5 ($La_2(CO_3)_3.4H_2O$) and Sample 6 ($La_2(CO_3)_3.3.8H_2O$) bind phosphate appreciably quicker than the $8.8H_2O$, $.1.3H_2O$ or $2.2H_2O$ forms. We believe that the results for $La_2(CO_3)_3.1.3H_2O$ are in agreement with the results shown in the above mentioned Japanese published patent application number 62-145024 where for $La_2(CO_3)_3.H_2O$, only 90% removal is shown after 120 minutes.

It can also be readily seen from Figure 1 of the accompanying drawings that the highest phosphate removal is obtained with lanthanum carbonates having 3 to 6 molecules of water.

The present invention offers the possibility of binding phosphate without any incursion of lanthanum into the blood stream, where toxic effects can cause problems. The specified lanthanum carbonate has negligible absorption from the gut, as shown by the *in vivo* tests described below.

Throughout this document, the term "treatment" is intended to include preventative treatment.

Processes for preparing lanthanum carbonates according to the present invention are described by way of illustration in the following Examples 1 and 2.

EXAMPLE 1

Lanthanum oxide (1.5kg, 4.58mol) was suspended in water (5.5 litres) in a 20 litre flask. Nitric acid (Analar grade, 69%, SG 1.42, 1.88 litres, 29.23mol) was added to the stirred solution over 1.5 hours at such a rate as to keep the temperature between 60-80°C. The resulting lanthanum nitrate solution was left to cool to room temperature and filtered. A solution of sodium carbonate (1.65kg, 15.57mol) in water (7.75 litres) was added to the stirred lanthanum nitrate solution over 45 minutes. At the end of the addition the pH of the suspension was 9.74. The suspension was left

overnight, filtered (Buchner funnel, 540 paper) and dried on the filter in a current of air for 30 minutes. The solid was then re-suspended in water, stirred for 40 minutes and filtered. This procedure was repeated to give a total of six washes, when the nitrate concentration in the filtrate was <500ppm. The final material (4.604kg) was divided between three Pyrex dishes and a sample from each analysed for water content. (By decomposition of weighed sample of $(La_2(CO_3)_3.xH_2O$ at 1050°C, 2 hours to La_2O_3). The dishes were then placed in a fan oven at 80°C and the weight loss of each dish monitored until the material of the required degree hydration was obtained. The progress of the drying is shown below

Time (hours)	mol H_2O/La		
	Dish 1	Dish 2	Dish 3
3.50	10.9	13.5	12.6
12	5.7	6.0	5.2
14	5.3	5.4	4.6
16	4.9	5.1	4.3
17	4.4	4.6	3.8
19.5	3.8	4.0	3.2

Drying curves for five batches produced by this route are shown in Figure 2.

$La_2(CO_3)_3.3.8H_2O$ from dish 1 was selected as Sample 6 for the phosphate binding tests set forth in Table 1.

EXAMPLE 2

The process of Example 1 was repeated but using hydrochloric acid (12.28M, 2.48 litres) in place of nitric acid to dissolve lanthanum oxide (1.5kg). The yield of crude product after six washes was 4.378kg. The product was divided in three approximately equal portions in Pyrex dishes and dried in a fan oven at 80°C. After 2 hours a sample was taken from each tray and water analysed by decomposition to lanthanum oxide as described above. These figures were used to calculate the weight loss needed to give material of the required composition. The time course of the drying process is shown below.

Time (hours)	mol H_2O/La		
	Dish 1	Dish 2	Dish 3
2	21.3	22.1	20.4
5.5	12.3	13.2	12.2
9	7.9	8.0	7.6
11.5	6.9	7.0	6.6
17	4.9	5.1	4.6
18.5	4.6	4.8	4.2
19.5	4.4	4.6	4.1
20	4.3	4.6	4.0

Samples were taken from each dish, combined and analysed. The following results were obtained:

	Found	Calculation for $La_2(CO_3)_3.4H_2O$
% La (gravimetric)	52.38%	52.4%
carbonate (titration)	5.76mol/g	5.66mol/g
H_2O (NMR)	13.06%	13.59%

The XRD analysis for lanthanum carbonate $4H_2O$ prepared by the method of Example 2 is illustrated in Figure 3.

Figure 4 illustrates the XRD of lanthanum carbonate $8.8H_2O$ and it is evident that it has a different crystalline structure from lanthanum carbonate $4H_2O$ prepared by the method of Example 2. The XRD analysis of lanthanum carbonate $4H_2O$ prepared by the method of Example 1 was similar to the XRD analysis of lanthanum carbonate $4H_2O$ prepared by the method of Example 2.

Pharmaceutical compositions for oral administration according to the invention may be formulated and manufactured using methods well known in the art. Suitable diluents or carriers are also well known. The compositions may desirably be in a dosage form, to provide a single daily dose, or a number of sub-daily dosages. Conventional pharmacological methods may be used to ascertain suitable dose levels. The level of phosphate in the food that an individual ingests is important. Daily dosages are indicated to be in the range 0.1 to 50g, preferably about 0.5 to 15g. Suitable forms for oral administration include solid forms such as tablets, capsules and dragees and liquid forms such as suspensions or syrups. In addition to diluents and carriers, it is conventional in the formulation of oral preparations to include non-active

ingredients such as thickeners, taste-improving components and colouring agents. The said carbonate may also be coated or treated to provide delayed-release forms. Preferably, the required daily dosage is given in tablet form, *eg* chewable tablet form, to be taken with meals. A suitable daily dosage of about 2g for 70kg man, should be compared with a daily dosage of 20g for a commercial calcium-based phosphate binding composition.

To demonstrate that the lanthanum carbonate of the invention (or lanthanum phosphate formed after binding to phosphate in the gut) is fully excreted and does not pass out of the gut into the circulation system when given orally, three rats were dosed with 20mg/kg of $La_2(CO_3)_3.4H_2O$ (Sample 5) and kept in metabolic cages where faeces and urine could be collected. The results are shown in Table 2 below.

Animal No.	Time (hours)	% La Recovered
1	24	103.2
1	48	0.1
1	72	<0.2
1	Total	103.3
2	24	75.3
2	48	23
2	72	1.2
2	Total	99.5

Animal No	Time (hours)	%La Recovered
3	24	93.8
3	48	10
3	72	0.1
3	Total	103.8

It can be seen that after 72 hours, all of the lanthanum has been excreted. In the urine samples, the amount of lanthanum was below detection limits. After the test, the rats were sacrificed, and kidney, liver and femur were analysed for lanthanum. In all cases, the amount of lanthanum was below 0.1ppm.

CLAIMS

1. A pharmaceutical composition for the treatment of hyperphosphataemia, comprising lanthanum carbonate of formula

$$La_2(CO_3)_3.xH_2O$$

where x has a value from 3 to 6, in admixture or association with a pharmaceutically acceptable diluent or carrier.

2. A composition according to claim 1, wherein in the lanthanum carbonate, x has a value from 3.5 to 5.

3. A composition according to claim 2, wherein in the lanthanum carbonate, x has a value from 3.8 to 4.5.

4. A composition according to any one of claims 1 to 3, in a form suitable for oral administration.

5. A composition according to any one of claims 1 to 4 in unit dosage form to provide from 0.1 to 20g/day.

6. The use of lanthanum carbonate as defined in any one of claims 1 to 3, for the preparation of a medicament for the treatment of hyperphosphataemia by administration into the gastrointestinal tract.

7. A process for the preparation of lanthanum carbonate as defined in any one of claims 1 to 3 which comprises the steps of:

(i) reacting lanthanum oxide with an acid which gives a soluble salt of lanthanum;

(ii) reacting a solution of the thus obtained lanthanum salt with an alkali metal carbonate to produce a wet cake of lanthanum carbonate octahydrate; and

(iii) controlled drying of the wet cake of lanthanum carbonate octahydrate so as to obtain a lanthanum carbonate with 3 to 6 molecules of water of crystallisation.

8. A process as claimed in claim 7 wherein the acid is nitric acid or hydrochloric acid.

9. A process as claimed in claim 7 or 8 wherein the alkali metal carbonate is sodium carbonate.

10. Lanthanum carbonate prepared according to the process of any of claims 7, 8 or 9.

11. Lanthanum carbonate of the formula

$$La_2(CO_3)_3.xH_2O$$

where x has a value from 3 to 6.

7. A process for the preparation of lanthanum carbonate as defined in any one of claims 1 to 3 which comprises the steps of:

(i) reacting lanthanum oxide with hydrochloric acid to obtain lanthanum chloride;

(ii) reacting a solution of the thus obtained lanthanum chloride with an alkali metal carbonate to produce a wet cake of lanthanum carbonate octahydrate; and

(iii) controlled drying of the wet cake of lanthanum carbonate octahydrate so as to obtain a lanthanum carbonate with 3 to 6 molecules of water of crystallisation.

8. A process as claimed in claim 7 wherein the alkali metal carbonate is sodium carbonate.

9. Lanthanum carbonate prepared according to the process of claim 7 or 8.

INTERNATIONAL SEARCH REPORT

[redacted]ional Application No
[redacted]/GB 96/00575

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K33/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C01F A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PATENT ABSTRACTS OF JAPAN vol. 011, no. 371 (C-462), 3 December 1987 & JP,A,62 145024 (ASAHI CHEM IND CO LTD), 29 June 1987, cited in the application see abstract ---	1-11
X	JOURNAL OF THE LESS-COMMON METALS, vol. 167, no. 2, 1 January 1991, pages 223-232, XP000202645 NAOHISA YANAGIHARA ET AL: "SYNTHESIS OF LANTHANIDE CARBONATES" see page 226; table 2 --- -/--	11

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search	Date of mailing of the international search report
13 August 1996	29.08.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Leherte, C

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 107, no. 26, 28 December 1987 Columbus, Ohio, US; abstract no. 249009, MINEELY, PATRICK J.; TARIQ, SHABBIR A.: "Molten potassium pyrosulfate: reactions of lanthanum metal and six of its compounds" XP002010788 see abstract & AUST. J. CHEM. (1987), 40(7), 1309-14, ---	11
X	CHEMICAL ABSTRACTS, vol. 104, no. 26, 30 June 1986 Columbus, Ohio, US; abstract no. 236218, MZAREULISHVILI, N. V.; NATIDZE, V. P.: " Study of interaction of lanthanum nitrate with alkali metal and ammonium carbonates" XP002010789 see abstract & SOOBSHCH. AKAD. NAUK GRUZ. SSR (1986), 121(1), 81-4, ---	11
X	CHEMICAL ABSTRACTS, vol. 87, no. 20, 14 November 1977 Columbus, Ohio, US; abstract no. 161013, ODA, TOSHIYUKI: "Studies on the crystal water of lanthanum carbonates" XP002010790 see abstract & OITA DAIGAKU KYOIKUGAKUBU KENKYU KIYO, SHIZEN KAGAKU (1975), 4(5),1-6, ---	11
X	CHEMICAL ABSTRACTS, vol. 87, no. 18, 31 October 1977 Columbus, Ohio, US; abstract no. 142122, KARAPET'YANTS, M. KH.; MAIER, A. I.; BAS'KOVA, N. A.: "Standard heats of formation of rare earth element and yttrium carbonates" XP002010791 see abstract & IZV. AKAD. NAUK SSSR, NEORG. MATER. (1977), 13(7), 1279-81, -----	11

Figure (s) to accompany abstract

PHARMACEUTICAL COMPOSITION AND METHOD

Abstract of the Invention

Selected lanthanum carbonate hydrates may be administered into the gastrointestinal tract, to treat hyperphosphataemia in patients with renal failure.